Claims

1. A device for delivery of a therapeutic agent to a treatment site comprising:

an outer layer adapted for placement of the device at an internal body site;

a reservoir within said outer layer, said reservoir adapted to form a closed system when containing a therapeutic agent;

a pressure equalization element adapted to maintain a substantially constant pressure within said closed system.

2. The device of claim 1 wherein the pressure equalization element comprises a membrane disposed within the outer layer, wherein the membrane divides the interior of the outer layer into a pressure equalizing chamber and a therapeutic agent chamber, wherein the volume of the pressure equalizing chamber changes in response to the volume in the therapeutic agent chamber in order to maintain a substantially constant pressure within the volume of the outer layer.

3. The device of claim 1 wherein the pressure equalization element comprises a channel.

4. The device of claim 2, further comprising a rate controlling membrane disposed between the membrane and the internal body surface.

5. The device of claim 1 wherein the outer layer further comprises an attachment element adapted for fixing said outer layer to an internal body surface.

6. The device of claim 5 wherein the attachment element comprises a rim.

7. The device of claim 6 further comprising a base that is contiguous with the rim and that contacts the internal body site and that has one or more openings

to allow a therapeutic agent contained within the reservoir to contact the body site.

8. The device of claim 2, wherein the membrane is flexible.

9. The device of claim 8, wherein the membrane comprises silicone, polyvinyl alcohol, ethylene vinyl acetate, polylactic acid, nylon, polypropylene, polycarbonate, cellulose, cellulose acetate, polyglycolic acid, polylactic glycolic acid, a cellulose ester, polyethersulfone, an acrylic, polytetrafluoroethylene, polyfluorinated ethylenepropylenesilastic, Dacron, Mylar, ionic salts of alginate, polycaprolactone, urethanes, polyethylene, polymethylmethacrylate, a polyester, or mixtures thereof.

10. The device of claim 2, further comprising a port through which a therapeutic agent can be injected into the therapeutic agent chamber.

11. The device of claim 10, wherein the port comprises first and second septa, wherein the first septum separates the exterior of the device from the pressure equalizing chamber, and wherein the second septum separates the pressure equalizing chamber from the therapeutic agent chamber.

12. The device of claim 11, wherein the first and second septa are disposed such that a needle is capable of piercing both septa simultaneously.

13. The device of claim 10, wherein the port comprises a valve.

14. The device of claim 11, wherein the septa comprise a resealable material through which the therapeutic agent can be injected.

15. The device of claim 14, wherein the material is selected from the group consisting of silicone, polyvinyl alcohol, ethylene vinyl acetate, cellulose, cellulose acetate, a cellulose ester, polyethersulfone, polytetrafluoroethylene, polyfluorinated

ethylenepropylenesilastic, Dacron, Mylar, polycaprolactone, urethanes, polyethylene, polymethylmethacrylate, a polyester, and mixtures thereof.

16. The device of claim 1, wherein the outer layer is comprised of a biocompatible, non-bioerodable material.

17. The device of claim 16, wherein the biocompatible, non-bioerodable material is selected from the group consisting of titanium, polypropylene, polyethylene, polycarbonate, polystyrene, polyester, urethane, nickel, nitinol, gold, tantalum, carbon, epoxy, and stainless steel.

18. The device of claim 1, further comprising a therapeutic agent disposed in the reservoir.

19. The device of claim 18, wherein the therapeutic agent is selected from the group consisting of small molecules, hormones, proteins, peptides, aptamers, lipids, DNA, RNA, PNA, enzymes, sugars, glycoproteins, polymers, metalloprotease, transition metals, antibodies, chelators, and combinations and prodrugs thereof.

20. The device of claim 19, wherein the therapeutic agent is an aptamer or prodrug thereof.

21. The device of claim 20, wherein the therapeutic agent is selected from the group consisting of anti-infectives; analgesics; antiallergenic agents; mast cell stabilizers; steroidal and non-steroidal anti-inflammatory agents; decongestants; anti-glaucoma agents; antioxidants; nutritional supplements; angiogenesis inhibitors; antimetabolites; fibrinolytics; wound modulating agents; neuroprotective drugs; angiostatic steroids; mydriatics; cyclopegic mydriatics; miotics; vasoconstrictors; vasodilators; anticlotting agents; anticancer agents; immunomodulatory agents; VEGF antagonists; immunosuppresant agents; and combinations and prodrugs thereof.

22. The device of claim 18, wherein the therapeutic agent is selected from the group consisting of 4,9(11)-pregnadien-17α,21-diol-3,20-dione, 4,9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate, timolol, betaxolol, atenolol, brimonidine, acetazolamide, methazolamide, dichlorphenamide, diamox, nimodipine, eliprodil, colchicine, vincristine, cytochalasin B, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, erythromycin, sulfonamides, sulfacetamide, sulfamethizole, sulfisoxazole, fluconazole, nitrofurazone, amphotericin B, ketoconazole, trifluorothymidine, acyclovir, ganciclovir, didanosine, AZT, foscamet, vidarabine, idoxuridine, ribavirin, protease inhibitors, anti-cytomegalovirus agents, methapyriline; chlorpheniramine, pyrilamine pheniramine, hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone, triamcinolone, phenylephrine, naphazoline, tetrahydrozoline, pilocarpine, carbachol, diisopropylfluorophosphate, echothiophate iodide, demecarium bromide, atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, epinephrine, heparin, antifibrinogen, fibrinolysin, anti clotting activase, acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin, aldose reductase inhibitors, thalidomide, 5-fluorouracil, adriamycin, asparaginase, azacytidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin, estramustine, etoposide, etretinate, filgrastim, floxuridine, fludarabine, fluoxymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, lomustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostim, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard, vinblastine, vindesine, pituitary hormones, insulin, insulin-related growth factor, thyroid hormones, growth hormones, heat shock proteins, muramyl dipeptide, interferons, interleukin-2, cytokines, FK506, tumor necrosis factor, thymopentin, transforming factor beta2, erythropoietin; antineogenesis proteins, monoclonal antibodies, brain nerve growth factor (BNGF), celiary nerve growth factor (CNGF), vascular endothelial growth factor (VEGF), monoclonal antibodies or aptamers directed against growth factors, and combinations and prodrugs thereof.

23. The device of claim 18, wherein the therapeutic agent is pegaptanib sodium.

24. The device of claim 1 further comprising a catheter having a first end in fluid communication with the reservoir and a second end adapted for placement at an administration site.

25. The device of claim 5, wherein the device is affixed to the sclera.

26. The device of claim 6 wherein the device is affixed to the sclera throughout the circumference of the rim.

27. A syringe for injecting fluid into or withdrawing fluid from a closed system, the syringe comprising:

a) a barrel having a fluid portal end and a pressure generating end;

b) a needle having a hollow bore and being connected to the fluid portal end;

c) a venting tube having a hollow bore and being connected to the needle, wherein the hollow bores of the venting tube and the needle are not in fluid communication; and

d) a pressure source connected to the pressure generating end of the barrel.

28. The syringe of claim 27, wherein the hollow bores of the needle and the venting are disposed coaxial to one another.

29. The syringe of claim 27, furthering comprising:

e) a vacuum source in fluid communication with the needle.

30. The syringe of claim 27, further comprising:

e) a second needle having a hollow bore that is not in fluid communication with the hollow bore of the needle; and

f) a vacuum source in fluid communication with the hollow bore of the second needle.

31. The syringe of claim 30, wherein the hollow bores of the needle and the second needle are coaxial to one another.

32. The syringe of 31, wherein the hollow bores of the needle, the second needle, and the venting tube are coaxial to one another.

33. The syringe of claim 29, wherein the vacuum source is an evacuated canister.

34. The syringe of claim 33, further comprising a window for viewing the interior of the canister.

35. The syringe of claim 33, wherein the evacuated canister is removable and sealable.

36. The syringe of claim 33, wherein the evacuated canister further comprises a flexible diaphragm.

37. The syringe of claim 28, wherein the pressure source is a plunger.

38. A method of injecting fluid into or withdrawing fluid from a closed system, the method comprising the steps of:

a) providing a syringe of claim 27;

b) passing the needle and venting tube through a port into the system; and

c) injecting fluid into or withdrawing fluid from the system,

wherein when fluid from the barrel is injected into the system through the needle, fluid inside the system exits through the venting tube in order to maintain a substantially constant pressure within the system, and when fluid from the system is pulled into the barrel through the needle, fluid outside the system enters the system through the venting tube in order to maintain a substantially constant pressure within the system.

39. The method of 38, wherein the closed system is a device comprising:

i) an outer layer adapted for placement on an internal body tissue so as to form a reservoir between said outer layer and said body tissue;

ii) a membrane disposed within the outer layer, wherein the membrane divides the interior of the outer layer into a pressure equalizing chamber and a therapeutic agent chamber, wherein the volume of the pressure equalizing chamber changes in response to the volume in the therapeutic agent chamber in order to maintain a substantially constant pressure within the volume of the outer layer; and

iii) an attachment element adapted for fixing said outer layer to an internal body surface that, when so affixed, defines a region which is in fluid communication with the therapeutic agent chamber;

wherein, in step (b), the needle is in fluid communication with the therapeutic agent chamber and the venting tube is in fluid communication with the pressure equalizing chamber; and

wherein when fluid from the barrel is injected into the therapeutic agent chamber through the needle, fluid inside the pressure equalizing chamber exits through the venting tube in order to maintain a substantially constant pressure within the device, and when fluid from the therapeutic agent chamber is pulled into the barrel through the needle, fluid outside the device enters the pressure equalizing chamber through the venting tube in order to maintain a substantially constant pressure within the device.

40. A method of injecting fluid into or withdrawing fluid from a closed system, the method comprising the steps of:

a) providing a syringe of claim 30;

b) passing the needle, the second needle, and the venting tube through a port into the system;

c) injecting fluid into or withdrawing fluid from the system;

wherein when fluid from the barrel is injected into the system through the needle, fluid inside the system exits through the venting tube in order to maintain a substantially

constant pressure within the system, and when fluid in the system is pulled into the vacuum source through the second needle, fluid from outside the system enters the system through the venting tube in order to maintain a substantially constant pressure within the system.

41. The method of 40, wherein the closed system is a device comprising:

i) an outer layer adapted for placement on an internal body tissue so as to form a reservoir between said outer layer and said body tissue;

ii) a membrane disposed within the outer layer, wherein the membrane divides the interior of the outer layer into a pressure equalizing chamber and a therapeutic agent chamber, wherein the volume of the pressure equalizing chamber changes in response to the volume in the therapeutic agent chamber in order to maintain a substantially constant pressure within the volume of the outer layer; and

iii) an attachment element adapted for fixing said outer layer to an internal body surface that, when so affixed, defines a region which is in fluid communication with the therapeutic agent chamber;

wherein, in step (b), the needle and the second needle are in fluid communication with the therapeutic agent chamber and the venting tube is in fluid communication with the pressure equalizing chamber; and

wherein when fluid from the barrel is injected into the therapeutic agent chamber through the needle, fluid inside the pressure equalizing chamber exits through the venting tube in order to maintain a substantially constant pressure within the device, and when fluid in the therapeutic agent chamber is pulled into the vacuum source through the second needle, fluid from outside the device enters the pressure equalizing chamber through the venting tube in order to maintain a substantially constant pressure within the device.

42. The method of claim 41, wherein step (c) comprises the steps of:

i) actuating the vacuum source to remove fluid from the therapeutic agent chamber; and

ii) increasing the pressure in the barrel to inject fluid into the therapeutic agent chamber.

43. The method of claim 38, wherein the fluid injected into the therapeutic agent chamber comprises a therapeutic agent.

44. The method of claim 43, wherein the therapeutic agent is selected from the group consisting small molecules, hormones, proteins, peptides, aptamers, lipids, DNA, RNA, PNA, enzymes, sugars, glycoproteins, polymers, metalloprotease, transition metals, antibodies, chelators, and combinations and prodrugs thereof.

45. The method of claim 43, wherein the therapeutic agent is an aptamer or prodrug thereof.

46. The method of claim 43, wherein the therapeutic agent is selected from the group consisting of anti-infectives; analgesics; antiallergenic agents; mast cell stabilizers; steroidal and non-steroidal anti-inflammatory agents; decongestants; anti-glaucoma agents; antioxidants; nutritional supplements; angiogenesis inhibitors; antimetabolites; fibrinolytics; wound modulating agents; neuroprotective drugs; angiostatic steroids; mydriatics; cyclopegic mydriatics; miotics; vasoconstrictors; vasodilators; anticlotting agents; anticancer agents; immunomodulatory agents; VEGF antagonists; immunosuppresant agents; and combinations and prodrugs thereof.

47. The method of claim 43, wherein the therapeutic agent is selected from the group consisting of 4,9(11)-pregnadien-17α,21-diol-3,20-dione, 4,9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate, timolol, betaxolol, atenolol, brimonidine, acetazolamide, methazolamide, dichlorphenamide, diamox, nimodipine, eliprodil, colchicine, vincristine, cytochalasin B, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, erythromycin, sulfonamides, sulfacetamide, sulfamethizole, sulfisoxazole, fluconazole, nitrofurazone, amphotericin B, ketoconazole, trifluorothymidine, acyclovir, ganciclovir,

didanosine, AZT, foscamet, vidarabine, idoxuridine, ribavirin, protease inhibitors, anti-cytomegalovirus agents, methapyriline; chlorpheniramine, pyrilamine pheniramine, hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone, triamcinolone, phenylephrine, naphazoline, tetrahydrozoline, pilocarpine, carbachol, diisopropylfluorophosphate, echothiophate iodide, demecarium bromide, atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, epinephrine, heparin, antifibrinogen, fibrinolysin, anti clotting activase, acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin, aldose reductase inhibitors, thalidomide, 5-fluorouracil, adriamycin, asparaginase, azacytidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin, estramustine, etoposide, etretinate, filgrastim, floxuridine, fludarabine, fluoxymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, lomustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostim, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard, vinblastine, vindesine, pituitary hormones, insulin, insulin-related growth factor, thyroid hormones, growth hormones, heat shock proteins, muramyl dipeptide, interferons, interleukin-2, cytokines, FK506, tumor necrosis factor, thymopentin, transforming factor beta2, erythropoietin; antineogenesis proteins, monoclonal antibodies, brain nerve growth factor (BNGF), celiary nerve growth factor (CNGF), vascular endothelial growth factor (VEGF), monoclonal antibodies or aptamers directed against growth factors, and combinations and prodrugs thereof.

48. The method of claim 43, wherein the therapeutic agent is pegaptanib sodium.

49. A method of treating an ocular disease state in a mammal, the method comprising the steps of:

a) affixing to the sclera of the eye of the mammal the device of claim 1, and

b) loading the device with a therapeutic agent that treats the disease state.

50. The method of claim 49, wherein the therapeutic agent is selected from the group consisting of small molecules, hormones, proteins, peptides, aptamers, lipids, DNA, RNA, PNA, enzymes, sugars, glycoproteins, polymers, metalloprotease, transition metals, antibodies, chelators, and combinations and prodrugs thereof.

51. The method of claim 49, wherein the therapeutic agent is an aptamer or prodrug thereof.

52. The method of claim 49, wherein the therapeutic agent is selected from the group consisting of anti-infectives; analgesics; antiallergenic agents; mast cell stabilizers; steroidal and non-steroidal anti-inflammatory agents; decongestants; anti-glaucoma agents; antioxidants; nutritional supplements; angiogenesis inhibitors; antimetabolites; fibrinolytics; wound modulating agents; neuroprotective drugs; angiostatic steroids; mydriatics; cyclopegic mydriatics; miotics; vasoconstrictors; vasodilators; anticlotting agents; anticancer agents; immunomodulatory agents; VEGF antagonists; immunosuppresant agents; and combinations and prodrugs thereof.

53. The method of claim 49, wherein the therapeutic agent is selected from the group consisting of 4,9(11)-pregnadien-17α,21-diol-3,20-dione, 4,9(11)-pregnadien-17α,21-diol-3,20-dione-21-acetate, timolol, betaxolol, atenolol, brimonidine, acetazolamide, methazolamide, dichlorphenamide, diamox, nimodipine, eliprodil, colchicine, vincristine, cytochalasin B, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, erythromycin, sulfonamides, sulfacetamide, sulfamethizole, sulfisoxazole, fluconazole, nitrofurazone, amphotericin B, ketoconazole, trifluorothymidine, acyclovir, ganciclovir, didanosine, AZT, foscamet, vidarabine, idoxuridine, ribavirin, protease inhibitors, anti-cytomegalovirus agents, methapyriline; chlorpheniramine, pyrilamine pheniramine, hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone, triamcinolone, phenylephrine, naphazoline, tetrahydrozoline, pilocarpine, carbachol, diisopropylfluorophosphate, echothiophate iodide, demecarium bromide, atropine sulfate, cyclopentolate,

homatropine, scopolamine, tropicamide, eucatropine, epinephrine, heparin, antifibrinogen, fibrinolysin, anti clotting activase, acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin, aldose reductase inhibitors, thalidomide, 5-fluorouracil, adriamycin, asparaginase, azacytidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin, estramustine, etoposide, etretinate, filgrastim, floxuridine, fludarabine, fluoxymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, lomustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostim, streptozocin, tamoxifen, taxol, teniposide, thioguanine, uracil mustard, vinblastine, vindesine, pituitary hormones, insulin, insulin-related growth factor, thyroid hormones, growth hormones, heat shock proteins, muramyl dipeptide, interferons, interleukin-2, cytokines, FK506, tumor necrosis factor, thymopentin, transforming factor beta2, erythropoietin; antineogenesis proteins, monoclonal antibodies, brain nerve growth factor (BNGF), celiary nerve growth factor (CNGF), vascular endothelial growth factor (VEGF), monoclonal antibodies or aptamers directed against growth factors, and combinations and prodrugs thereof.

54. The method of claim 49, wherein the therapeutic agent is pegaptanib sodium.

55. The method of claim 49, wherein the therapeutic agent is admixed with a pharmaceutically acceptable carrier adapted to provide sustained release of the therapeutic agent.

56. The method of claim 55, wherein the carrier is selected from the group consisting of emulsions, suspensions, polymeric matrices, microspheres, microcapsules, microparticles, liposomes, multivesicular liposomes, lipospheres, hydrogels, salts, and polymers with the therapeutic agent reversibly bound electrostatically, chemically or by entrapment.

57. The method of claim 56, wherein the pharmaceutically acceptable carrier comprises a transscleral diffusion promoting agent.

58. The method of claim 57, wherein the promoting agent is selected from the group consisting of dimethylsulfoxide, ethanol, dimethylformamide, propylene glycol, N-methylpyrolidone, oleic acid, isopropyl myristate, polar aprotic solvents, polar protic solvents, steroids, sugars, polymers, small molecules, charged small molecules, lipids, peptides, proteins, and surfactants.

59. The method of claim 49, wherein the affixing comprises suturing, gluing, or sealing by means of one or more polymerizable compounds.

60. The method of claim 46, wherein the affixing comprises utilizing a biological healing mechanism.

61. The method of claim 60, wherein the biological healing mechanism is a postoperative adhesion, fibrotic encapsulation, or other foreign body reaction.

62. The method of claim 49, wherein step (b) is carried out two or more times with the same device.

63. The method of claim 49, wherein the device is affixed to the sclera over the equator of the eye.

64. The method of claim 49, wherein the device is affixed to the sclera over the pars planar of the eye.

65. The method of claim 49, wherein the disease state is macular degeneration, diabetic retinopathy, glaucoma, optic disc neovascularization, iris neovascularization, retinal neovascularization, choroidal neovascularization, pannus, pterygium, macular edema, vascular retinopathy, retinal vein occlusion, histoplasmosis, ischemic retinal

disease, retinal degeneration, uveitis, inflammatory diseases of the retina, keratitis, cytomegalovirus retinitis, an infection, conjunctivitis, cystoid macular edema, cancer, or proliferative vitreoretinopathy.

66. The method of claim 65, wherein the disease state is macular degeneration.

67. The method of claim 49, wherein the therapeutic agent is delivered to the choroid or retina.

68. The method of claim 56 wherein the therapeutic agent comprises pegaptanib sodium.